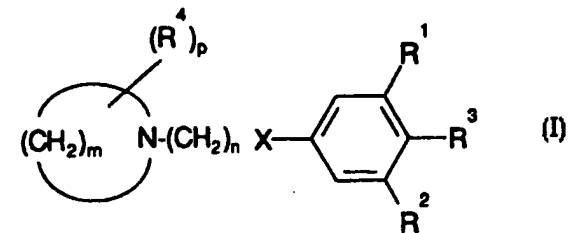


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<p>(21) International Application Number: PCT/EP93/03629</p> <p>(22) International Filing Date: 16 December 1993 (16.12.93)</p> <p>(30) Priority Data: 9226718.6 22 December 1992 (22.12.92) GB 9321808.9 22 October 1993 (22.10.93) GB</p> <p>(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex 9EP TW8 (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KING, Ronald, Joseph [GB/GB]; Smithkline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). BROWN, Thomas, Henry [GB/GB]; Smithkline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). COOPER, David, Gwyn [GB/GB]; Smithkline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).</p> <p>(74) Agent: FLORENCE, Julia, A.; Corporate Intellectual Property, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).</p>	<p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: PIPERIDINE DERIVATIVES AS CALCIUM CHANNEL ANTAGONISTS</p>		
<p>(57) Abstract</p> <p>Compounds of formula (I): wherein R¹ represents C₁-alkyl, halogen or phenyl; R², represents hydrogen, C₁-alkyl, halogen or phenyl; R³ represents hydroxyl or a group convertible thereto <i>in vivo</i>; R⁴ represents C₁-alkyl; p is zero, 1 or 2; X represents -CH₂-, -C(=O)-, O or S; n is an integer from 4 to 10; m is an integer from 3 to 8; and salts thereof are useful as calcium antagonists, e.g. in the treatment of conditions relating to an accumulation of calcium in brain cells.</p> <div style="text-align: right;">  <p>(I)</p> </div>		

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PIPERIDINE DERIVATIVES AS CALCIUM CHANNEL ANTAGONISTS

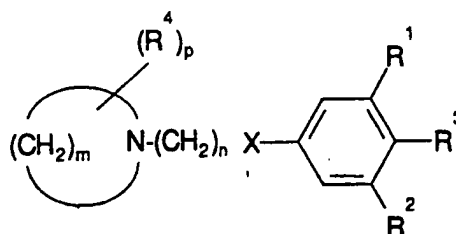
The present invention relates to heterocyclic compounds, processes for preparing them, their use in therapy and pharmaceutical compositions containing them.

5 EP-A-190685 describes heterocyclic amides which are said to be anti-inflammatory and anti allergy agents.

EP-A-476846 describes known phenols and benzamides for use inter alia in preventing ischaemia-induced cell damage.

10 We have now found that certain heterocyclic derivatives containing a phenol moiety exhibit activity as calcium channel antagonists and radical scavengers.

In a first aspect therefore the present invention provides compounds of formula (I) :



Formula (I)

wherein

R¹ represents C₁₋₆alkyl, halogen or phenyl;

R² represents hydrogen, C₁₋₆alkyl, halogen or phenyl;

20 R³ represents hydroxyl or a group convertible thereto *in vivo* ;

R⁴ represents C₁₋₆alkyl;

p is zero, 1 or 2;

X represents -CH₂-, -C=O, O or S;

n is an integer from 4 to 10;

25 m is an integer from 3 to 8;

and salts thereof.

Alkyl groups present in the compounds of formula (I) may be straight or branched. When R¹ and/or R² represents C₁₋₆alkyl this may be for example a methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, sec-pentyl, 1,1-dimethylpropyl, or
30 n-hexyl group. R¹ and R² preferably represent branched alkyl groups, most preferably t-butyl.

Groups R³ which are convertible *in vivo* to hydroxyl (also referred to as bioprecursors or physiologically functional equivalents) include C₁₋₄alkoxy; C₁₋₄alkanoyloxy e.g. acetoxy; aryl C₁₋₄alkanoyloxy e.g. phenyl C₁₋₄alkanoyloxy such as

benzoyloxy; aryl sulphonyloxy e.g. optionally substituted phenylsulphonyloxy such as toluene sulphonyloxy or C₁₋₄alkylsulphonyloxy e.g. methylsulphonyloxy.

n is preferably 5 to 8.

m is preferably 4 to 6.

5 p is preferably zero.

It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, and tartrate salts, and base salts such as alkali metal e.g. sodium or potassium salts. Other non-pharmaceutically acceptable salts e.g. oxalates, may be used for example in the isolation of the final product and are included within the scope of this invention.

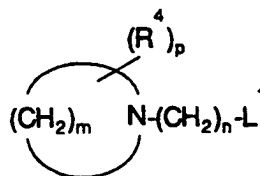
It will be appreciated that the compounds of formula (I) may contain one or more asymmetric centres. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

Particular compounds according to the invention include :

1-[6-oxo-6-(4-hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine,
 20 1-[8-oxo-8-(4-hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine,
 1-[6-(4-Hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine,
 1-[8-(4-Hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine,
 1-[7-(4-Hydroxy-3,5-di-tert-butyl)thiophenoxy-heptyl]piperidine,
 1-[7-(4-Hydroxy-3,5-di-tert-butyl)phenoxyheptyl]piperidine,
 25 1-[7-Oxo-7-(4-hydroxy-3,5-di-tert-butylphenyl)heptyl]piperidine,
 and salts thereof.

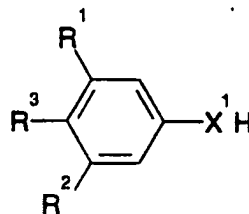
The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect, a process for the preparation of a compound of formula (I) which comprises:

30 (a) to prepare a compound (I) wherein X is O or S, reaction of a compound of formula (II):



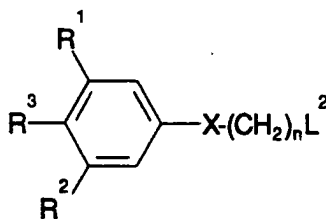
Formula (II)

in which m , n , R^4 and p are as defined in formula (I) and L^1 is a group displaceable with a nucleophile with a compound of formula (III) :



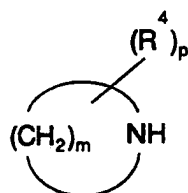
Formula (III)

- 5 in which X^1 is O or S and R^1 , R^2 and R^3 are as defined in formula (I); or
(b) reaction of a compound of formula (IV) :



Formula (IV)

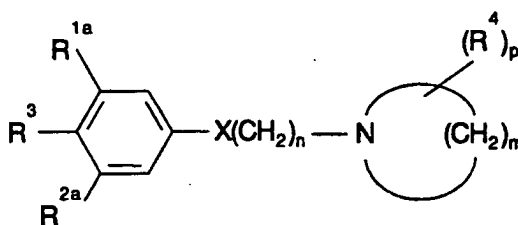
- 10 in which R^1 , R^2 , R^3 , X and n are as defined for formula (I) and L^2 is a leaving group with a compound of formula (V) :



Formula (V)

in which m , R^4 and p are as defined in formula (I);

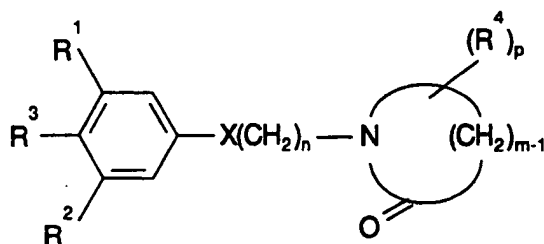
- (c) introduction of the groups R^1 and/or R^2 by reaction of a compound of
15 formula (VI) :



Formula (VI)

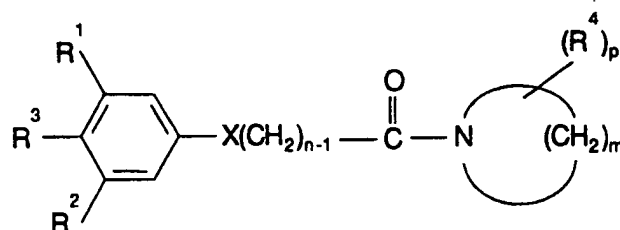
- (wherein one of R^{1a} and R^{2a} is hydrogen and the other is selected from hydrogen,
halogen, C_{1-6} alkyl or phenyl, and R^3 , R^4 , X , n , m and p are as defined for formula (I))
20 with a compound serving to introduce R^1 and/or R^2 ;

(d) to prepare a compound where X is -CH₂-, S or O, reduction of an amide of formula (VII) or (VIII) :



Formula (VII)

5



Formula (VIII)

(e) conversion of a compound of formula (I) to a different compound of formula (I) for example, reduction of a compound (I) wherein X is C=O to a compound wherein X is -CH₂-; or reaction of a compound wherein R² is hydrogen according to process (c) to give a compound wherein R² is other than hydrogen; followed if desired by salt formation.

In process (a) the reaction between a compound of formula (II) and a compound of formula (III) can be carried out under standard conditions. For example when L¹ is hydroxy, the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine. Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L¹ may be for example a halogen atom or a sulphonyloxy group e.g. methane-sulphonyloxy or p-toluene sulphonyloxy. In this case the reaction may be effected in the absence or presence of solvent such as dimethylformamide or methylethylketone in the presence of a base such as sodium hydride or potassium carbonate and at a temperature in the range 0 to 200°C.

The reaction of a compound of formula (IV) with a compound of formula (V) according to process (b) may be effected in conventional manner, for example using excess amine as solvent or alternatively using an organic solvent, such as dichloromethane or dimethyl formamide. The leaving group L² may be for example a halide such as bromide or chloride, an acyloxy group such as acetoxy or chloroacetoxy or a sulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy. The reaction may

optionally be carried out in the presence of a base such as sodium hydride or potassium t-butoxide.

In process (c) the groups R^1 and R^2 may be introduced by standard methods. Thus for example a halo substituent may be introduced by reaction with the appropriate halogen e.g. Br_2 or I_2 . An alkyl group e.g. t-butyl may be introduced by reaction with isobutylene $(CH_3)_2C=CH_2$. This method may be used to prepare compounds wherein R^1 and R^2 are not identical.

Reduction of an amide according to process (d) may be effected using a suitable reducing agent such as lithium aluminium hydride and an inert solvent such as diethyl ether or tetrahydrofuran. Reduction of a compound (I) wherein X represents $C=O$ according to process (e) may be effected similarly. It will be appreciated that when X in formula (VII) or (VIII) represents $C=O$ this will be reduced simultaneously.

The compounds of formula (II) can be prepared under standard alkylation conditions by reacting compounds of formula (IX) :



in which L^1 , L^2 and n are as hereinbefore defined, with compounds of formula (V) as hereinbefore defined. The reaction is suitably carried out under analogous conditions to those described above for process (b).

It will be appreciated that in compounds of formula (IX) the leaving groups L^1 and L^2 are preferably selected so that the compound of formula (V) reacts selectively with L^2 . For example, in a compound of formula (IX) L^1 is suitably hydroxy and L^2 is suitably halo.

Compounds of formula (III) may be prepared using standard procedures well known in the art.

Compounds of formula (IV) where X is O or S can be prepared by reacting a compound of formula (III) as hereinbefore defined with a compound of formula (IX) as hereinbefore defined. In this reaction both L^1 and L^2 can be identical, for example halo such as bromo. The reaction is suitably carried out in the presence of a weak base such as potassium carbonate. Alternatively the reaction may be carried out under phase transfer conditions, for example using benzyltriethylammonium chloride in the presence of a strong base such as sodium or potassium hydroxide.

Compounds of formula (IV) where X is $C=O$ may be prepared by Friedel Craft acylation of the appropriate substituted phenyl derivative with an acylating agent of the formula $Hal-C(O)-(CH_2)_nL^2$. Preferably Hal represents chloro and L^2 represents bromo. The reaction may be effected using standard conditions, for example in a solvent such as

dichloromethane. The Friedel Craft catalyst may be for example aluminium trichloride or stannic chloride.

Compounds of formula (V) are commercially available and may be prepared by standard literature methods.

5 Compounds of formula (VI) may be prepared according to one of the general methods (a), (b) or (d) described herein.

Compounds of formula (VII) may also be prepared according to the general processes described herein, e.g. processes (a), (b) or (c).

10 Compounds of formula (VIII) may be prepared by acylation of a compound of formula (V), for example with an appropriate acid chloride or ester, which may itself be prepared from a compound of formula (IV) by standard methods. Alternatively a compound (VIII) may be prepared by a method analogous to process (a).

Compounds of formula (IX) are commercially available or may be prepared by standard methods.

15 When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

20 The compounds of the invention have been found to exhibit high calcium influx blocking activity for example in neurons. As such the compounds are expected to be of use in therapy in treating conditions and diseases related to an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction
25 withdrawal such as ethanol addiction withdrawal.

The compounds also have antioxidant properties and are therefore expected to be useful in the treatment of conditions in which free radicals are implicated, for example prevention of ischemic cell damage.

30 The invention also provides a method of treatment of conditions or diseases caused or exacerbated by the accumulation of calcium in the brain cells of mammals which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof.

35 Thus for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect the invention also provides the use of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition in which free radicals are implicated and/or in the manufacture of a medicament for the treatment of a condition or disease caused or exacerbated by the accumulation of calcium in the brain cells of a mammal.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may be administered by any convenient method for example by oral, parenteral, buccal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as cyclodextrins.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, e.g. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

Ca²⁺ Current Measurement

Cell preparations

Sensory neurons from dorsal root ganglia were dissociated from 1 day old rat pups (Ford et al, Developmental Brain Research, 22 (1985), 55-65). Cells were plated out onto glass coverslips and used within 3 days to permit effective voltage clamp of Ca²⁺ currents.

Solutions

The pipette (internal solution) contained in mM: CsCl, 130; HEPES, 10; EGTA, 10; MgCl₂, 4; ATP, 2; buffered to pH 7.2 with CsOH. Cells were bathed in a normal Tyrodes solution before establishment of whole cell recording when the bathing solution was changed to one allowing isolation of Ca²⁺ currents.

30

The external solution for recording Ca²⁺ channel currents contained in mM: BaCl₂, 10; TEA-Cl, 130; glucose, 10; HEPES, 10; MgCl₂, 1; buffered to pH 7.3 with TEA-OH. Barium was used as the charge carrier as this assists in current isolation and calcium dependent inactivation of current is avoided. Compounds were dissolved in DMSO to make a 20 mM stock solution. At the drug concentration used the vehicle (0.1%) had no significant effect on Ca²⁺ currents. All experiments were performed at 21 to 24°C. Whole cell currents were recorded using List EPC-7 amplifiers and stored, digitised for

later analysis using PC based software similar to that described previously (Benham & Tsien, Journal of Physiology (1988), 404, 767-784).

RESULTS

5 Ca²⁺ currents

Peak voltage gated Ca²⁺ channel currents of up to 10 nA from dorsal root ganglion neurons were recorded using 10 mM Ba²⁺ as charge carrier. Currents were evoked from a holding potential of -80 mV to a test potential of 0 or +10 mV every 15 seconds. This test potential was at the peak of the current voltage relationship and assessing block at this point reduced any errors due to drifting holding potential. Some cells showed slow
10 rundown of current as is commonly seen when recording Ca²⁺ currents. The rundown rate was measured in control conditions and extrapolated through the time of drug application to derive a control value to relate the drug affected current to. Block by 20 μ M drug was assessed 3 minutes after drug application.

15

Compounds of the invention gave percentage inhibition of plateau Ca²⁺ current of greater than 60%.

Preparation 1

20 1-[6-oxo-6-(4-hydroxy-3,5-di-tert-butylphenyl)hexyl]bromide

2,6-Di-tert-butylphenol (5.15g) and 6-bromohexanoyl chloride (4.2ml) were stirred together in anhydrous dichloromethane (40ml). The reaction mixture was cooled to -70°C and stannic chloride (5.9ml) in anhydrous dichloromethane (75ml) was added dropwise. The reaction mixture was stirred for 1h. Water was added and the mixture extracted with
25 ether. The organic phase was washed with water and dried with anhydrous sodium sulphate. The solvent was removed *in vacuo* and the product purified by silica chromatography using hexane/ether mixtures as elutant. The **title compound** was obtained (8.47g 89%) M.P. 78-82°C

30 Preparation 2

1-[8-oxo-8-(4-hydroxy-3,5-di-tertbutylphenyl)octyl]bromide

Substituting 8-bromooctanoylchloride (0.65g) for 6-bromohexanoylchloride in Preparation 1 above and using appropriate molar quantities of the other reagents gave the **title compound** (1.10g quantitative yield) M.P. 115-118°C.

35

Preparation 3**7-(4-Hydroxy)-3,5-di-tert-butylthiophenoxy-1-bromoheptane**

A mixture of water (240ml) and dichloromethane (21ml) were stirred together under argon. Sodium hydroxide (0.4g, 10 mmol) was added and stirred until dissolved.

- 5 Benzyltriethyl-ammonium chloride (11.78g, 51.7 mmol), dibromoheptane (4.32g 16.7 mmol) and 2,6-di-tert-butyl-4-mercaptothiophenol (2g, 8.4 mmol; EPA 190682) were added and the reaction mixture heated until the internal temperature reached 60°C. The temperature was maintained until the reaction was complete. The mixture was allowed to cool and dichloromethane (80ml) was added. The organic phase was separated, washed
10 with brine and dried over sodium sulphate. Solvent was removed *in vacuo*. The resulting oil was purified by silica chromatography using hexane as elutant to give the title compound (3.90g) in quantitative yield.

Mass spectroscopy gave a mass ion m/z :416 (M^+)

15 **Preparation 4**

2,6-Di-tert-butyl-1,4-benzohydroquinone

- 2,6-Di-tert-butyl-1,4-benzoquinone (5g, 22.7 mmol) was stirred in hexane (250ml) and acetic acid (90ml) under argon. Zinc powder (10g) was added over 30min. The reaction mixture was left to stir for 1h. The reaction mixture was filtered and the filtrate washed
20 with a dilute solution of sodium hydrosulphite. The hexane solution was extracted with 5% sodium hydroxide solution containing a trace of sodium hydrosulphite. Acidification of the basic extract with hydrochloric acid gave a solid which was collected by filtration. Recrystallisation of this solid from hexane gave the title compound (2.724g, 54%) m.p. 103-105°C.

25

Preparation 5**7-(4-Hydroxy-3,5-di-tert-butyl)phenoxy-1-bromo-heptane**

A mixture of water (240ml) and dichloromethane (25ml) were stirred under argon. Sodium hydroxide (0.54g, 13.5 mmol) was added and stirred until dissolved.

- 30 Benzyltriethylammonium chloride (16.05g, 70.5 mmol), dibromoheptane (5.94g, 23.0 mmol) and 2,6-di-tert-butyl-1,4-benzohydroquinone (2.724g, 12.3 mmol) were added. The reaction mixture was heated until an internal temperature of 60°C had been achieved. The mixture was then refluxed for 16h. Dichloromethane (80ml) was added and the mixture stirred for 10min. The organic phase was separated, washed with brine and dried
35 over sodium sulphate. The solvent was removed *in vacuo* and the residue purified by

silica chromatography using dichloromethane as elutant. The **title compound** (6.24g) was obtained as an oil.

Preparation 6

5 7-Bromoheptanoyl chloride

ω -Bromoheptanoic acid (9.0g, 43.0 mmol) was stirred and heated with thionyl chloride (5ml) at 100°C for 96h. The mixture was allowed to cool and toluene (50ml) was added. The solvent was removed *in vacuo*. Kugelrohr distillation of the residue gave the **title compound** (8.79g) b.p. 145° at 0.03mbar.

10

Preparation 7

1-[7-Oxo-7-(4-hydroxy-3,5-di-tert-butylphenyl)heptyl]bromide

2,6-Di-tert-butylphenol (7.06g, 34.2 mmol) was stirred under argon in dichloromethane at -70°C. 7-Bromoheptanoyl chloride (7.79g, 34.2 mmol) in dichloromethane (40ml) was
15 added. Stannic chloride (8ml) in dichloromethane (50ml) was added over approx. 30min. The reaction mixture was stirred at -70°C for 4h. Ice cold water (50ml) was added and the mixture extracted with ether. The ether solution was washed with brine, dried over sodium sulphate and the solvent removed *in vacuo*. The residue, an oil, was purified by silica chromatography using hexane: ether (9:1) as elutant. This gave the **title compound**
20 (12.19g) as an oil.

Example 1

1-[6-oxo-6-(4-hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine hydrochloride

Piperidine (1ml) was added to 1-[6-oxo-6-(4-hydroxy-3,5-di-tert-butylphenyl)hexyl]bromide (0.71g) in anhydrous dichloromethane and stirred under
25 nitrogen at room temperature for four days. The reaction mixture was washed successively with dilute hydrochloric acid, aqueous sodium hydroxide and water. After drying with sodium sulphate the solvent was removed *in vacuo*. The product was dissolved in anhydrous ether and treated with a slight excess of 1M hydrogen chloride in
30 ether. The resulting solid was collected by filtration and recrystallised from ethylacetate/methanol mixture to give the **title compound** (0.40g 54.1%). M.P. 161-166°C.

Found : C, 69.13%; H, 9.55%; N, 3.29%; Cl, 8.22% ($C_{25}H_{41}NO_2 \cdot HCl \cdot 0.5 H_2O$) requires C, 69.33%; H, 10.00%; N, 3.23%; Cl, 8.19%.

35

Example 2

1-[8-oxo-8-(4-hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine hydrochloride

Piperidine (1.30ml) was added to 1-[8-oxo-8-(4-hydroxy-3,5-di-tert-butylphenyl)octyl]bromide (1.05g) in anhydrous dichloromethane (20ml). The mixture was stirred under nitrogen at room temperature until the reaction was complete. The reaction mixture was washed successively with dilute hydrochloric acid, aqueous sodium hydroxide and water. After drying with anhydrous sodium sulphate, the solvent was removed *in vacuo*. The product was dissolved in anhydrous ether and treated with a slight molar excess of ethereal hydrogen chloride. The resulting solid was collected by filtration and recrystallised from ethyl acetate/methanol mixtures to give the title compound (0.41g 36%) M.P. 160-162°C

Found: C, 71.54%; H, 9.89%; N, 2.93%; Cl, 8.34% ($C_{27}H_{45}NO_2HCl$) requires C, 71.73%; H, 10.26%; N, 3.10%; Cl, 7.84%

Example 3

1-[6-(4-Hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine hydrochloride

Lithium aluminium hydride (9.71g) suspended in anhydrous diethyl ether (100ml) and a solution of 1-[6-oxo-6-(4-hydroxy-3,5-bis-tert-butylphenyl)hexyl] piperidine (2.0g) in anhydrous diethyl ether (20ml) was added dropwise. The reaction was left to stir at room temperature for two days. The reaction mixture was treated with brine. The ether layer was separated, dried with anhydrous sodium sulphate and the solvent removed *in vacuo*. The product was dissolved in anhydrous ether and treated with a slight molar excess of hydrogen chloride in ether. The resulting solid was collected by filtration and recrystallised from ethyl acetate to give the title compound (0.37g, 17%) M.P. 152-153°C

Found: C, 72.81%; H, 10.37%; N, 3.38%; Cl, 8.28% ($C_{25}H_{43}NO.HCl$) requires C, 73.22%; H, 10.81%; N, 3.42%; Cl, 8.65%

Example 4

1-[8-(4-Hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine hydrochloride

Lithium aluminium hydride (0.20g) was suspended in anhydrous diethyl ether (70ml) and a solution of 1-[8-oxo-8-(4-hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine (0.43g) in anhydrous diethyl ether (5ml) was added dropwise. The reaction was left to stir at room temperature for two days. The reaction mixture was treated with brine. The organic phase was dried with anhydrous sodium sulphate and the solvent removed *in vacuo*. The product was dissolved in anhydrous ether and treated with a slight molar excess of hydrogen

chloride in diethyl ether. The resulting solid was collected by filtration and recrystallised from ethyl acetate/methanol to give the **title compound** (0.40g 89%) M.P. 145-146°C
 Found: C, 73.68%; H, 10.59%; N, 3.20%; Cl, 8.68% ($C_{27}H_{47}NO.HCl$)
 requires C, 74.02%; H, 11.04%; N, 3.20%; Cl, 8.09%

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Example 5

1-[7-(4-Hydroxy-3,5-di-tert-butyl)thiophenoxyheptyl]piperidine hydrochloride

7-(4-Hydroxy-3,5-di-tert-butyl) thiophenoxy-1-bromoheptane (3.41g, 8.2 mmol) was stirred under argon with an 80% oil dispersion of sodium hydride (0.26g, 10.8 mmol) in anhydrous dimethylformamide. Piperidine (0.8ml) was added over 10min and the reaction mixture heated at 60°C for 16h. The reaction mixture was cooled to room temperature and partitioned between water and diethyl ether. The organic phase was evaporated. The residue was dissolved in dichloromethane and agitated with an excess of 50% V/V hydrochloric acid. The organic phase was washed with brine, dried over sodium sulphate and evaporated *in vacuo*. The resulting oil was purified by silica chromatography using dichloromethane/methanol mixtures as elutant. The product was recrystallised from ethyl acetate to give the **title compound** (0.334g, 10% yield), M.Pt. 122-123°C
 Found: C, 68.14; H, 9.79; N, 3.09; Cl, 7.65% ($C_{26}H_{45}NOS.HCl$)
 requires C, 68.46; H, 10.16; N, 3.07; Cl, 7.77%

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Example 6

1-[7-(4-Hydroxy-3,5-di-tert-butyl)phenoxyheptyl]piperidine hydrochloride

7-(4-Hydroxy-3,5-di-tert-butyl)phenoxy-1-bromoheptane (6.24g, 15.6 mmol) was stirred with piperidine (45ml) in dichloromethane (70ml) under argon for 48h. The reaction mixture was washed with 5% aqueous sodium hydroxide and brine and dried over sodium sulphate. The solvent and excess piperidine were removed *in vacuo*. The resulting oil was purified by silica chromatography using dichloromethane (90): methanol (10): aqueous ammonia (1), as elutant. The product was dissolved in dichloromethane and washed with 50% V/V hydrochloric acid. The organic phase was separated and dried over sodium sulphate. The solvent was removed *in vacuo* and the resulting oil crystallised from isopropyl acetate to give the **title compound** (0.769g) m.p. 166-167°C.
 Found: C, 70.96; H, 10.54; N, 3.18; Cl, 8.06% ($C_{26}H_{45}NO_2.HCl.0.25H_2O$)
 requires C, 70.50; H, 10.24; N, 3.32; Cl, 8.08%

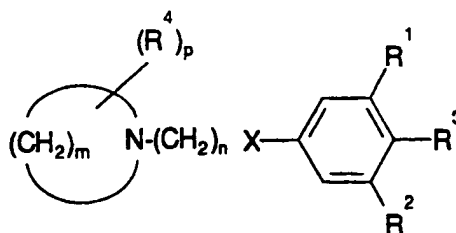
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Example 7**1-[7-Oxo-7-(4-hydroxy-3,5-di-tert-butylphenyl)heptyl]piperidine hydrochloride**

- 1-[7-Oxo-7-(4-hydroxy-3,5-di-tert-butylphenyl)heptyl]bromide (12.10g, 30.4 mmol) was stirred in dichloromethane (100ml). Piperidine (15.5ml) was added and the mixture stirred at room temperature for 48h. The reaction mixture was washed with water and dried over sodium sulphate. Solvent was removed *in vacuo* to give an oil which crystallised on trituration with ether. The product was purified by recrystallisation from ethyl acetate/methanol to give the **title compound** (6.371g) m.p. 165-167°C.
- Found: C, 70.88; H, 9.89; N, 3.30; Cl, 7.76% (C₂₆H₄₅NO.HCl.)
- requires C, 71.28; H, 10.12; N, 3.20; Cl, 8.09%

Claims

1. A compound of formula (I) :



Formula (I)

wherein

R^1 represents C_{1-6} alkyl, halogen or phenyl;

R^2 represents hydrogen, C_{1-6} alkyl, halogen or phenyl;

R^3 represents hydroxyl or a group convertible thereto *in vivo* ;

R^4 represents C_{1-6} alkyl;

p is zero, 1 or 2;

X represents $-CH_2-$, $-C=O$, O or S;

n is an integer from 4 to 10;

m is an integer from 3 to 8;

or a salt thereof.

2. A compound according to claim 1 wherein one or both of R^1 and R^2 represents a branched C_{1-6} alkyl group.

3. A compound according to either claim 1 or claim 2 wherein p represents zero.

4. A compound according to any of claims 1 to 3 wherein n is an integer from 5 to 8.

5. A compound according to any of claims 1 to 4 wherein m is an integer from 4 to 6.

6. A compound of formula (I) selected from:

1-[6-oxo-6-(4-hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine,
1-[8-oxo-8-(4-hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine,
1-[6-(4-Hydroxy-3,5-di-tert-butylphenyl)hexyl]piperidine,

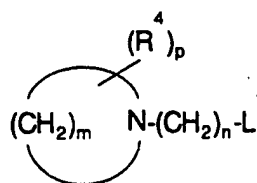
1-[8-(4-Hydroxy-3,5-di-tert-butylphenyl)octyl]piperidine,
 1-[7-(4-Hydroxy-3,5-di-tert-butyl)thiophenoxy-heptyl]piperidine,
 1-[7-(4-Hydroxy-3,5-di-tert-butyl)phenoxyheptyl]piperidine,
 1-[7-Oxo-7-(4-hydroxy-3,5-di-tert-butylphenyl)heptyl]piperidine,

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or a salt thereof.

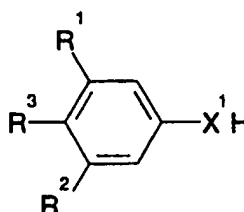
7. A process for the preparation of a compound of formula (I) as hereinbefore defined, which process comprises:

10 (a) to prepare a compound (I) wherein X is O or S, reaction of a compound of formula (II):



Formula (II)

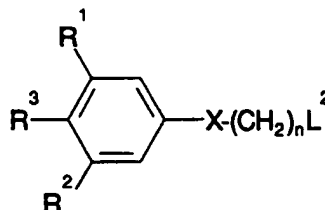
15 in which m, n, R^4 and p are as defined in formula (I) and L^1 is a group displaceable with a nucleophile with a compound of formula (III) :



Formula (III)

in which X^1 is O or S and R^1 , R^2 and R^3 are as defined in formula (I); or

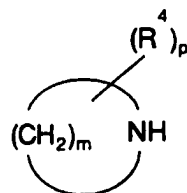
(b) reaction of a compound of formula (IV) :



Formula (IV)

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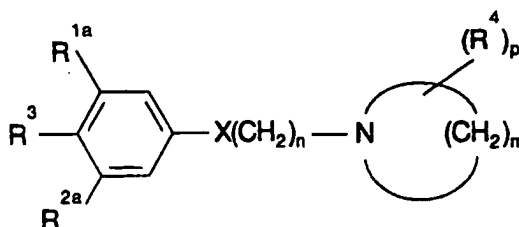
in which R^1 , R^2 , R^3 , X and n are as defined for formula (I) and L^2 is a leaving group with a compound of formula (V) :



Formula (V)

in which m , R^4 and p are as defined in formula (I);

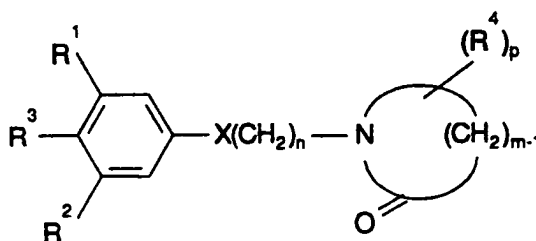
- (c) introduction of the groups R^1 and/or R^2 by reaction of a compound of formula (VI):



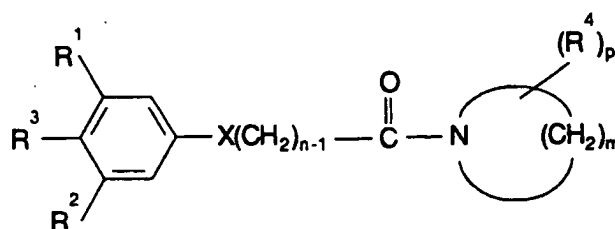
Formula (VI)

- (wherein one of R^{1a} and R^{2a} is hydrogen and the other is selected from hydrogen, halogen, C_{1-6} alkyl or phenyl, and R^3 , R^4 , X , n , m and p are as defined for formula (I)) with a compound serving to introduce R^1 and/or R^2 ;

- (d) to prepare a compound where X is $-CH_2-$, S or O , reduction of an amide of formula (VII) or (VIII):



Formula (VII)



Formula (VIII)

- (e) conversion of a compound of formula (I) to a different compound of formula (I);

followed if desired by salt formation.

8. A method of treatment of a condition in which free radicals are implicated, which comprises administering to a subject in need thereof an effective amount
5 of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof.

9. A method of treatment of a condition or disease caused or exacerbated by the accumulation of calcium in the brain cells of a mammal which comprises
10 administering to a subject in need thereof an effective amount of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof.

10. Use of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the
15 treatment of a condition in which free radicals are implicated.

11. Use of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition or disease caused or exacerbated by the accumulation of calcium
20 in the brain cells of a mammal.

12. A pharmaceutical composition comprising a compound of formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D295/10 C07D295/08 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 103 252 (BASF AKTIENGESELLSCHAFT) 21 March 1984 *Document*	1-7
A	EP,A,0 164 706 (BASF AKTIENGESELLSCHAFT) 18 December 1985 *Document*	1-7
A	WO,A,88 06580 (SCHERING AKTIENGESELLSCHAFT) 7 September 1988 *Document*	1-12
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

11 April 1994

Date of mailing of the international search report

20.04.94

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Authorized officer

Luyten, H

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 112, no. 19, 7 May 1990, Columbus, Ohio, US; abstract no. 178818, page 753 ;column R ; see abstract & IZV. AKAD. NAUK SSSR, SER. KHIM. no. 11 , 1989 , RUSSIA pages 2580 - 2585 SAKHAROVA, S.N. ET. AL. ---	1-7
A	CHEMICAL ABSTRACTS, vol. 111, no. 21, 20 November 1989, Columbus, Ohio, US; abstract no. 194691e, page 766 ;column R ; see abstract & KHIM. GETEROSIKL. SOEDIN. no. 11 , 1988 , RUSSIA KARAULOVA, E. N . ET. AL. ---	1-7
P,A	WO,A,93 00313 (VIRGINIA COMMONWEALTH UNIVERSITY) 7 January 1993 *Page 101-103: compound 161,164,169* *Page 143-200:claims* -----	1-12

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8 and 9 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0103252	21-03-84	DE-A- 3233828	15-03-84
EP-A-0164706	18-12-85	DE-A- 3421810 JP-A- 61044863 US-A- 4705553	12-12-85 04-03-86 10-11-87
WO-A-8806580	07-09-88	DE-A- 3706585 EP-A- 0346367 JP-T- 2502376	08-09-88 20-12-89 02-08-90
WO-A-9300313	07-01-93	AU-A- 2294592 CA-A- 2111957	25-01-93 07-01-93